



# Expanded Access

**Compounding Advisory Committee Meeting  
June 17-18, 2015**

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CDER/FDA**

# Investigational New Drug (IND) – A Safeguard for Patients

- FDA's role in the regulation of novel medicines was born out of tragedy: **71 adults and 34 children died** in the fall of 1937 after taking a drug called Elixir Sulfanilamide for a variety of ailments.
- IND applications allow FDA to review information on investigational **drugs** before they are administered to humans.
- IND submissions and investigator responsibilities are key parts of regulatory requirements to protect patient safety
  - FDA review of chemistry, manufacturing, and animal toxicology studies
  - Investigational review board (IRB) review
  - Informed consent

# What is Expanded Access?

Treatment access to investigational drugs (including biologics) outside of a clinical trial setting for patients with serious/life-threatening diseases (or conditions) when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

# What Is a *Serious Condition*?

## (21 CFR 312.300(b))

- “. . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning”
- Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent.
- Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”

# Expanded Access: General Information

- Facilitates availability of investigational drugs for patients with serious or life-threatening diseases
- Potential patient benefit justifies the potential risk of the treatment use; risks are not unreasonable in the context of the disease or condition
- Expanded access cannot jeopardize drug development
  - drug development and drug approval provide the greatest evidence of risk-benefit information and the best access to the most number of patients
- No prohibitions against use of multiple investigational agents under expanded access

# Expanded Access to Investigational Drugs for Treatment Use

## Regulation 21 CFR Part 312, Subpart I

- In effect since 2009, but similar processes predate this
- Establishes three categories of expanded access
  - Individual (including for emergency use)
  - Intermediate-size patient populations
  - Treatment IND/protocol (widespread treatment use)
- More evidence of efficacy needed as number of people receiving treatment increases
- Establishes parameters and outlines filing requirements

# Weighing Safety and Risk for Individual Patients

## 21 CFR 312.310



- Licensed physician may make the request and may become the IND holder (investigator) when drug sponsor chooses not to hold IND
- Physician determines probable risk from drug does not exceed that from disease or condition
- FDA determines that the patient cannot obtain the drug under another IND or protocol
- Non-emergency or emergency use may be granted
- Additional safeguards
  - Treatment generally limited to one course unless authorized by FDA
  - FDA may request consolidation of multiple cases into single, intermediate-size patient population IND



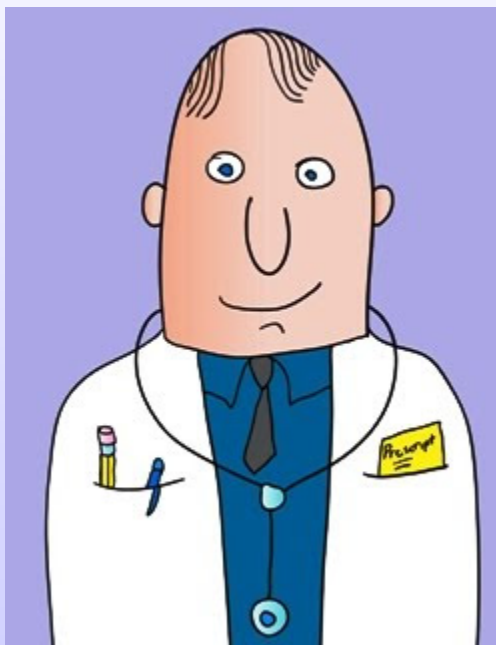
# Weighing Safety and Risk for Intermediate-Size Population

## 21 CFR 312.315

- Usually, drug sponsor (or manufacturer) is IND holder
- May be needed when drug is:
  - Not being developed (e.g., disease rare)
  - Being developed but patients are not eligible for ongoing clinical trials
  - Approved drug that is not available (e.g., drug withdrawn, drug shortage)
- Sufficient evidence drug is safe at proposed dose and duration to justify size of exposed population
- Preliminary evidence of efficacy
- Additional safeguards
  - Require explanation of why drug cannot be developed or why patients cannot be enrolled in clinical trial
  - Annual review to determine whether treatment use should be continued and whether a Treatment IND would be a more appropriate mechanism

# Single-Patient INDs

## *“Nuts and Bolts”*



“I’m a physician who  
needs an investigational  
drug for my patient with a  
serious illness.

What do I do?”

## Expanded access for individual patients, including for emergency use

- Identify sponsor (or manufacturer) of drug and ask them if they will provide access and to have product shipped
  - Permission should include the sponsor letting FDA refer to its IND or files previously submitted to FDA
- Contact FDA (phone, fax or email) to request an IND.
  - For emergency INDs, FDA available by phone 24/7
  - Non-emergency, usually accomplished during business hours.
- When IND allowed to proceed:
  - For emergency use: fill out paperwork later and obtain IND# during business hours, company ships drug on verbal agreement from FDA
  - Single patient IND: fill out paperwork, obtain IND#, and provide # to drug sponsor. FDA has 30 days to review, technically, but often granted the same day!

## **FDA Contacts – Normal Business Hours (8 am – 4:30 pm EST weekdays)**

For Drugs, CDER's Division of Drug Information (DDI) at:

- Phone: 301-796-3400 or 855-543-3784;
- Fax: 301-431-6353;
- E-mail: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov).
- Can also contact specific review division, if known

# FDA Contacts – After Hours

(after 4:30 or Weekends/Holidays)

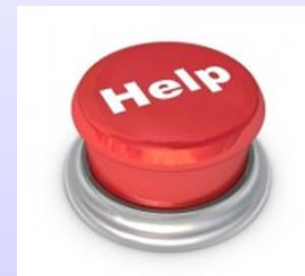
- FDA Emergency Call Center
- Telephone: 866-300-4374



# Paperwork

## Review Division Can Help You

- 2015 draft guidance issued on simplified draft form: Form 3926. Soon physicians will be able to use this one-page, user-friendly form 3926 for initial individual patient expanded access submissions.
- Using old forms: often can be accomplished in an hour (or two) or less.
- Form 1571 (basic information needed)
  - Regarding requestor (name, address)
  - Name of product and source
  - Patient's disease course and need for drug (no names)
  - Planned treatment course (dose, duration) and monitoring
  - Technical and preclinical information about product supplied by drug sponsor (manufacturer) via letter of authorization (LOA)
- Form 1572 (physician information/credentials, can attach CV)



# Sponsor-Investigator Responsibilities

- If for emergency use: inform IRB within 5 working days
- If non-emergency, obtain IRB approval before treating patient
- Obtain informed consent
- Submit any unexpected, serious adverse reactions that are considered related to drug to FDA
- At the conclusion of treatment, provide FDA with a written summary of the results of the expanded access use, including adverse effects
- If dosing for a year or more submit an annual report to FDA

## Summary Points

- Explanation of processes and parameters for expanded access are clearly outlined in 21 CFR 312, Subpart I and are further explained on FDA's website:  
[http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm#How\\_To\\_Apply](http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm#How_To_Apply)
- 2015 draft guidance further simplifies procedures for investigator-initiated sINDs: New abbreviated draft form 3926
- FDA contacts are available 24/7 to assist physicians in the process of submitting a single patient IND, including for emergency use
- Regulatory responsibilities of the investigator are in place to protect the safety of the patient

# **Process for Identifying Candidates for, or Amendments to, the Withdrawn or Removed List**

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Gail Bormel  
Acting Director, Division of Prescription Drugs  
Office of Unapproved Drugs and Labeling Compliance  
CDER**

# Drugs on the Withdrawn or Removed List

- Under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA is to publish a list of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective (the withdrawn or removed list).
- Drugs on the withdrawn or removed list cannot qualify for the exemptions under sections 503A and 503B.
- The background for this list was described in the briefing information for the February 2015 PCAC meeting, available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm431285.htm>.

## Section 503A

- 503A describes the conditions under which certain compounded human drug products are entitled to exemptions from three requirements of the FD&C Act:
  - FDA approval prior to marketing (section 505)
  - Compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B))
  - Labeling with adequate directions for use (section 502(f)(1))
- Pharmacies that qualify for these exemptions are primarily regulated by the states, although some Federal requirements still apply (e.g., no insanitary conditions)

# Compounding Quality Act of the Drug Quality and Security Act

- Adds new section 503B: “Outsourcing Facilities”
- Registered outsourcing facilities
  - Must comply with CGMP requirements
  - Will be inspected by FDA according to a risk-based schedule
  - Must meet certain conditions to be exempt from the new drug approval requirements, the requirement that product labeling bear adequate directions for use, and the drug supply chain security requirements in section 582 of the FD&C Act

# Process for Identifying Drugs for the Withdrawn or Removed List *(cont.)*

- FDA periodically reviews available information on drugs withdrawn or removed from the market because they have been found to be unsafe or not effective with the goal of identifying possible new candidate drugs for the list.
- The information reviewed may include:
  - *Federal Register* notices announcing withdrawal of approval of a drug application for safety or effectiveness reasons
  - *Federal Register* notices announcing an Agency determination that a drug product was removed from sale for reasons of safety or effectiveness

# Process for Identifying Drugs for the Withdrawn or Removed List *(cont.)*

Other information reviewed by the Agency may include:

- FDA Alerts
- FDA Drug Safety Communications
- FDA news releases
- Public Health Advisories
- Dear Healthcare Practitioner letters
- Citizen petitions
- Sponsor letters

# Process for Identifying Drugs for the Withdrawn or Removed List *(cont.)*

FDA also periodically reviews available information to determine whether any new drug applications have been approved for a drug product containing as an active ingredient any of the drugs on the list to determine whether any of the drug entries on this list should be modified to account for this new safety and effectiveness determination and approval.

# Examples

- For example, a drug may have been approved in a new formulation, indication, route of administration, or dosage form since the list was last revised.
- If so, FDA might consider proposing a modification to the list to remove the drug from the list or to exclude the particular formulation, indication, route of administration, or dosage form.

# Process for Identifying Drugs for the Withdrawn or Removed List *(cont.)*

- Appropriate divisions within the Office of New Drugs (OND) evaluate each identified candidate or proposed modification using the available information about the drug.
- The responsible division will prepare a review of the information that documents its recommendations as to whether to include the drug on the withdrawn or removed list, or remove a drug from the list, or modify an entry.

# Process for Updating the Withdrawn or Removed List

In the past, FDA has published a notice of proposed rulemaking to add identified drug products to the list or modify existing entries before consulting the Advisory Committee.

- October 8, 1998, *Federal Register*: A proposed rule identified 60 drug products for the list; FDA consulted the Advisory Committee prior to finalizing the rule.
- July 2, 2014, *Federal Register*: A proposed rule identified 25 drugs to add to the list and one entry to modify on the original list (codified at 21 CFR 216.24). FDA invited comments on the appropriate procedure to update the list in the future. In February 2015, FDA consulted the Advisory Committee on the drugs identified in the July proposed rulemaking notice.

# Updates for the Withdrawn or Removed List

- As stated in the July 2 *Federal Register* Notice, the Agency is considering its process for updating the withdrawn or removed list going forward and will announce that process in the final rule.
- For the June 2015 meeting, there are four newly identified drug candidates for the Advisory Committee to review which may eventually be included in an update to the list.

# June 2015 Meeting – Drugs Identified for the Withdrawn or Removed List

FDA is considering for inclusion on the list the 4 drugs listed below.

1. **Acetaminophen** – All drug products containing more than 325 milligrams of acetaminophen per dosage unit
2. **Aprotinin** – All drug products containing aprotinin
3. **Ondansetron hydrochloride** – All intravenous drug products containing greater than a 16 milligram, single dose of ondansetron hydrochloride
4. **Bromocriptine mesylate** – All drug products containing bromocriptine mesylate for prevention of physiological lactation

# Acetaminophen

**Pharmacy Compounding Advisory Committee Meeting  
June 17, 2015**

**Sharon Hertz, M.D.  
Division Director**

**Division of Anesthesia, Analgesia, and Addiction Products  
FDA/CDER**

# Acetaminophen

- One of the most commonly used drugs in the US for treating pain and fever
- Hydrocodone–acetaminophen combination products – the most frequently prescribed drug since 1997
- Exceeding the maximum daily dose of 4 grams of acetaminophen places patients at risk for serious liver injury and death
- Acetaminophen-related hepatotoxicity – leading cause of acute liver failure in the US

# Factors Leading to Acetaminophen-Related Liver Failure

- Given the large number and wide array of OTC and prescription acetaminophen products and indications, consumers have unintentionally overdosed by taking more than one acetaminophen-containing drug product at the same time without realizing that acetaminophen is a common ingredient.
- Patients are often unaware that their prescription analgesics contain acetaminophen, often identified on pharmacy drug containers only as “APAP,” an acronym based on the chemical name of acetaminophen (N-acetyl-para-aminophenol), or by an abbreviation such as “ACET.”

# Factors Leading to Acetaminophen-Related Liver Failure (*cont.*)

- Patients may take more than the maximum number of labeled or prescribed doses seeking additional therapeutic benefit, unaware that they are taking too much acetaminophen.
- The symptoms of liver damage can take several days to emerge and are not readily recognized as the result of acetaminophen poisoning by patients or clinicians.
- The antidote for acetaminophen overdose, N-acetylcysteine (NAC), is most effective when given in the first 8 hours after an acute overdose, with benefit up to 24 hours and possibly later.

# Factors Leading to Acetaminophen-Related Liver Failure *(cont.)*

- Although experts agree that taking a large amount of acetaminophen over a short period of time causes liver injury, a specific threshold dose for toxicity has not been established and may not be the same for all persons.
- All of the factors that might increase an individual's risk of acetaminophen toxicity have not been identified, particularly at doses near the current recommended total daily dose of 4,000 mg per day.

# FDA Actions to Reduce Acetaminophen-Induced Liver Injury

- 2002 - Advisory Committee members agreed that labeling changes were warranted for acetaminophen-containing products
- 2004 - FDA engaged in public education campaign. FDA asked state boards of pharmacy to require: use of “acetaminophen,” not “APAP”; instruct patients on safe use (i.e., not to use multiple products with acetaminophen, not to exceed maximum daily dose, avoid concurrent alcohol use).
- 2006 - FDA proposed regulations for OTC labeling - safety information, container and outer carton to clearly identify acetaminophen.
- 2007- CDER set up working group for next steps, leading to 2009 AC meeting.

# Advisory Committee Meeting

## June 29 and 30, 2009

- Data presented:
  - No evidence that, when in combination, 325 mg provides substantially more efficacy than 500 mg
  - Reduction from 500 mg to 325 mg per dosage unit would reduce risk
  - Intentional overdose:
    - 72% took up to 25 pills\*
    - 12.5 g at 500 mg per pill vs. 8.1 g at 325 mg/pill
  - Unintentional overdose:
    - 39% knowingly took more than recommended amount\*
    - Mean dose associated with hepatotoxicity 6.5 g/day\*\*
    - With 325 mg limit, would have been 4.2 g/day

\*Dan Budnitz, Acetaminophen-related Emergency Department Visits, National Electronic, Injury Surveillance System

\*\* Office of Surveillance and Epidemiology, Characterization of Acetaminophen Overdose and Related Hepatotoxic Events

# Recent Regulatory History of Acetaminophen

- After the AC meeting, FDA concluded that acetaminophen prescription drugs containing more than 325 mg of acetaminophen per dosage unit (tablet or capsule) do not provide sufficient margin of safety to protect the public against the serious risk of acetaminophen-induced liver injury
  - *Federal Register* on January 14, 2011 (76 FR 2691)

## Recent Regulatory History (*cont.*)

- All product sponsors asked to:
  - Limit maximum amount of acetaminophen per dosage unit to 325 mg
  - Submit requests that FDA withdraw approval of applications for products with more than 325 mg acetaminophen under 21 CFR 314.150(d) by January 14, 2014.
- Withdrawal of approvals completed on July 17, 2014.

# Recommendation

- Because approvals of applications for prescription drug products containing more than 325 milligrams of acetaminophen per dosage unit have been withdrawn by FDA for safety reasons, FDA recommends the following entry for acetaminophen be added to the withdrawn or removed list:

*Acetaminophen: All drug products containing more than 325 milligrams of acetaminophen per dosage unit.*

# Aprotinin

**Pharmacy Compounding Advisory Committee Meeting  
June 17, 2015**

**Kathy Robie Suh, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
FDA/CDER**

# Outline

- Aprotinin background
  - Description
  - Indication
  - Safety profile
- Regulatory history of aprotinin
- Rationale for FDA conclusion that aprotinin was removed from the market because it was found to be unsafe

# Aprotinin Description and Use

- Proteinase inhibitor derived from beef lung
- MW-6512 Daltons; 58 amino acids
- Modulates the systemic inflammatory response, fibrinolysis and thrombin generation
- Administered intravenously
- Metabolized with a half-life of 150 minutes
- Use: (1993) prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing CPB in the course of CABG surgery who are at increased risk for blood loss and blood transfusion

# Major Adverse Reactions Associated with Aprotinin

- Hypersensitivity reactions, including anaphylaxis, with deaths reported, particularly after re-exposure (Boxed Warning)
- Renal dysfunction
- Death with a frequency greater than other antifibrinolytics used during CABG with CPB

# Regulatory History

- January, 2006 - NEJM publication reports more adverse reactions with the use of aprotinin compared to aminocaproic acid, tranexamic acid or no antifibrinolytic therapy in CABG with CPB
- September, 2006 - Meeting of Cardiovascular and Renal Products AC
- September, 2006 - Revelation of i3 study (Published 2008)
- September, 2007 - Joint meeting of Cardiovascular and Renal Products and the Drug Safety and Risk Management ACs
- October, 2007 - BART trial halted for increase mortality in the aprotinin-treated arm
- November, 2007 - Sponsor agrees to remove aprotinin from marketing worldwide. Sponsor arranged for continued access to aprotinin for use in certain surgical patients with an established medical need via an open-label treatment protocol.

# NEJM Publication

January, 2006 - NEJM publication<sup>1</sup> of an observational study of risk associated with aprotinin in cardiac surgery

- Retrospective analysis of aprotinin compared to 2 other antifibrinolytic drugs (tranexamic acid and aminocaproic acid) or no antifibrinolytic drugs in 4,374 patients undergoing cardiac surgery.
- Found a statistically greater likelihood of the development of renal dysfunction and the need for hemodialysis, stroke, encephalopathy, myocardial infarction and congestive heart failure in patients treated with aprotinin than with the other antifibrinolytic drugs or no antifibrinolytic drugs.

<sup>1</sup> Mangano DT, Tudor IC, and Dietzel C. The risk associated with aprotinin in cardiac surgery. N Engl J Med. 2006; 354(4):353-5

## i3 Study

Hospital database analysis (Premier Perspective Comparative Database) for period April 2003 through March 2006; published February 2008<sup>3</sup>

- Conducted at the request of the manufacturer
- Retrospective analysis evaluated a medical database for the outcomes of patients undergoing CABG treated with aprotinin or other antifibrinolytics.
- Concluded that there was an increased risk of in-hospital death in the aprotinin treated patients compared to those in patients treated with aminocaproic acid.

<sup>3</sup> Schneeweiss S, Seeger JD, Landon J, and Walker AM. Aprotinin during coronary artery bypass graft surgery and the risk of death. N Engl J Med. 2008; 358:771-783.

## BART Study

Initiated August 2002; Terminated October 2007; published 2008<sup>3</sup> -

- Prospective randomized trial of aprotinin, tranexamic acid and aminocaproic acid in patients undergoing CABG with CPB in Canada
- Terminated early upon recommendation of the Data Monitoring and Safety Committee due to finding that there appeared to be a greater frequency of death in patients treated with aprotinin (6.0%) compared to those treated in the combined tranexamic acid plus aminocaproic acid group (3.9%)

<sup>3</sup> Fergusson DA, Hébert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008;358:2319-31.

# Regulatory History

- January, 2006 - NEJM publication reports more adverse reactions with the use of aprotinin compared to aminocaproic acid, tranexamic acid or no antifibrinolytic therapy in CABG with CPB
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# Conclusion and Recommendation

- Conclusion: Aprotinin was removed from the market because it was found to be unsafe due to:
  - Renal adverse events
  - Deaths due to anaphylaxis
  - Improvement in safety of blood supply with respect to infection risk
  - Increase in deaths with use of aprotinin compared to that with both aminocaproic acid and tranexamic acid
- Recommendation for list:

Aprotinin: All drug products containing aprotinin

# **Intravenous Ondansetron Hydrochloride**

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Karyn L. Berry, MD, MPH  
Medical Officer**

**Division of Gastroenterology and Inborn Errors Products  
FDA/CDER**

# Outline

- Ondansetron Background
  - Description
  - Indications
- Recent regulatory history
- Rationale for FDA determination that intravenous ondansetron 32 mg\* dose was withdrawn from the market because it was found to be unsafe

**\*Intravenous ondansetron remains approved and still marketed in the U.S. at lower doses (no single dose to exceed 16 mg)**

# Description

- Initially approved in 1991 as ZOFTRAN
- Selective 5-HT<sub>3</sub> receptor antagonist
- Extensively metabolized - ~ 5% of radiolabeled dose recovered as parent compound from urine
- Primary metabolic pathway is hydroxylation on the indole ring, followed by glucuronide or sulfate conjugation
- Mean elimination half-life in normal adult volunteers (aged 19-40 yrs) - 3.5 h

# Description *(cont.)*

- **Labeled Indications**

- Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy
- Prevention of postoperative nausea and vomiting

# Recent Regulatory History

- September 15, 2011 – FDA issued Drug Safety Communication:
  - Concerned that the anti-nausea drug Zofran (ondansetron, ondansetron hydrochloride and their generics) may increase risk of cardiac arrhythmias, such as QT prolongation, which could be serious and lead to sometimes fatal heart rhythm called Torsades de Pointes.
- FDA required applicant holder of ZOFRAN (ondansetron) to conduct a thorough QT trial.
- June 29, 2012 – FDA issued a Drug Safety Communication:
  - Preliminary results from the thorough QT trial suggested a 32 mg single IV dose of ondansetron could prolong the QT interval, which could pre-dispose patients to develop Torsades de Pointes

# Thorough QT trial

- A double-blind, single IV dose, placebo and positive controlled cross-over trial in 58 healthy subjects
- Study demonstrated that ondansetron prolonged the QT interval in a dose dependent manner
  - The maximum mean difference in QTcF from placebo after baseline correction was 19.5 ms after 15 min IV infusion of ondansetron 32 mg and 5.6 ms after 15 min IV infusion of ondansetron 8 mg
- Analysis of data demonstrated that 32 mg single IV ondansetron dose significantly prolonged the QT interval
- Additional analyses of these data were useful in determining the maximum safe and effective intravenous dosing for ondansetron intravenous formulation

# Recent Regulatory History *(cont.)*

- November 14, 2012 – Professional labeling for ZOFTRAN was changed to:
  - remove the recommendation for a 32 mg single IV dose;
  - add statements that ondansetron IV could continue to be used in adults and children for CINV at a lower IV dose; however, **no single IV dose should exceed 16 mg.**
- December 4, 2012 - FDA issued Drug Safety Communication notifying HCP that the 32 mg single IV dose of ondansetron would no longer be marketed because of the potential for serious cardiac risk.
  - FDA worked with manufacturers of all ondansetron injectable products (brand and generic) to change the professional label by removing or recalling the single 32 mg IV dose from the market.
- Based on potential of 32 mg single IV dose of ondansetron to prolong the QT interval, FDA determined that the single 32 mg IV dose was withdrawn for reasons of safety.

# Recommendations

- Listing
  - Entry for the withdrawal or removal list:
    - **Ondansetron hydrochloride: All intravenous drug products containing greater than a 16 milligram, single dose of ondansetron hydrochloride.**
- Rationale for determination
  - Risk of QT prolongation is greater with 32 mg single IV ondansetron dose compared to single IV ondansetron doses of  $\leq 16$  mg
  - Data analysis demonstrated that lower single doses (i.e.,  $\leq 16$  mg IV ondansetron) are safe and effective for the prevention of CINV in adults and children compared to safety profile of 32 mg single IV dose
  - **No single IV ondansetron dose should exceed 16 mg**
  - Oral formulations of ondansetron expected to lead to lower max level of drug in bloodstream compared to IV admin; therefore no dosing changes recommended

# **Parlodel (bromocriptine mesylate) Tablets, USP and Capsules**

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Christine P. Nguyen, M.D.  
Deputy Director for Safety  
Division of Bone, Reproductive, and Urologic Products  
OND/CDER/FDA**

# Outline

- Parlodel (bromocriptine mesylate) description
- Regulatory history of Parlodel
- Major safety concerns with Parlodel use for lactation suppression
- Overview of FDA's determination and action leading to withdrawal of Parlodel for **Prevention of Physiological Lactation\*** for reasons of safety

\*Parlodel is currently approved and marketed in the US for other indications.

# Parlodel Description

- An ergot derivative with potent dopamine receptor agonist activity that inhibits prolactin secretion
- Prolactin inhibition prevents physiological lactation in women when Parlodel is started after delivery and continued for 2-3 weeks postpartum

# Regulatory History

- 1978 - Parlodel was approved.
- 1980 - through an efficacy supplement, Parlodel was approved for **Prevention of Physiological Lactation.**

# Parlodel:

## Currently Approved Indications

- Hyperprolactinemia-associated Dysfunctions
- Acromegaly
- Parkinson's Disease

# Major Safety Concerns\*

## with Parlodel use for lactation suppression

- After the 1980 approval of the lactation suppression indication, cases were reported postmarket of serious adverse reactions and deaths associated with Parlodel when used for lactation suppression. The reports included:
  - Hypertension
  - Seizures
  - Cerebrovascular accidents
  - Myocardial infarction
- By 1989, FDA had received 85 postmarket reports of serious adverse events and 10 deaths.

\* Food and Drug Administration [Docket No. 94N-0304] Sandoz Pharmaceuticals Corp.; Bromocriptine Mesylate (Parlodel) for the Prevention of Physiological Lactation; Opportunity for a Hearing on a Proposal To Withdraw Approval of the Indication, Federal Register, 59(162):43347-43352, 1994 (August 23).

# Major Safety Concerns *(cont.)*

- At a 1989 meeting, an Advisory Committee (AC) recommended that “no drug labeled for lactation suppression, including Parlodel (bromocriptine mesylate), be used for this indication.”
- After the 1989 AC meeting, FDA asked that all manufacturers of drugs containing bromocriptine mesylate voluntarily remove the indication because the risks of hypertension, seizures, and cardiovascular accidents outweighed the product’s marginal benefit in preventing postpartum lactation.

# Regulatory Action

- FDA published a notice in the *Federal Register* on January 17, 1995 (60 FR 3404), announcing the withdrawal of Parlodel's indication for the prevention of physiological lactation for reasons of safety.
- The withdrawal became effective on February 16, 1995.\*

*\*Food and Drug Administration [Docket No. 94N-0304] Sandoz Pharmaceuticals Corp.; Bromocriptine mesylate (Parlodel); Withdrawal of Approval of the Indication for the Prevention of Physiological Lactation.*

# Rationale for FDA Determination

- Lactation is a self-limiting condition; the ability to lactate disappears if a woman does not breast feed.
- Breast engorgement and its associated discomfort prior to the complete suppression of lactation is a non-serious condition.
- Breast engorgement and discomfort may be adequately treated with non-pharmacologic measures, such as breast binding and mild analgesics.
- Given the reports of serious adverse events when used for this purpose, there was an unacceptable benefit-risk balance for the suppression of lactation indication.

# **Process For Developing the 503A Bulk Drug Substances List**

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Jane A. Axelrad  
Associate Director for Policy, CDER  
and Agency Lead on Compounding**

## Conditions for Bulk Drug Substances Used to Compound Under 503A

- Bulk drug substances (i.e., generally, active ingredients) used to compound must:
  - Comply with the standards of an applicable US Pharmacopoeia (USP) or National Formulary (NF) monograph, if one exists, and the USP chapters on pharmacy compounding;
  - Be a component of an FDA-approved drug, if an applicable USP or NF monograph does not exist; **or**

## Conditions for Bulk Drug Substances Used to Compound Under 503A, *cont.*

- If neither of the above, the substances must be on a list, developed by FDA through regulation, of bulk drug substances acceptable for compounding.
- All bulk drug substances used in compounding must be made at a facility registered with FDA under section 510 of the Food, Drug, and Cosmetic Act (FD&C Act) and be accompanied by a valid Certificate of Analysis (COA).

## Process for Developing 503A List

- December 2013 – Nominations solicited
- July 2, 2014 - FDA re-solicited nominations for the list; 740 unique substances nominated
- Many were already components of FDA-approved drugs or the subject of a USP monograph, and therefore not candidates for the list
- Some nominated substances were not supported by sufficient information to allow FDA to evaluate the substance
- FDA has preliminarily identified 64 substances for evaluation

# Factors FDA Considers In Prioritizing Substances For Review

- Safety concerns about use of the bulk drug substance in compounding;
- Whether the bulk drug substance was nominated by multiple parties or identified as necessary by medical professional organizations;
- The efficiency with which the evaluation can be completed, based on ease of acquiring the necessary information to conduct the review, available resources, and other logistical issues.
- FDA may group some nominated drug substances to facilitate efficient review and discussion (e.g., drugs that are nominated for the treatment of the same condition).

## Review Process

- FDA consults experts (chemists, toxicologists, clinicians) in the review divisions to evaluate the substances, and the reviewers prepare reviews.
- FDA presents reviews to the PCAC.
- FDA considers the recommendations of PCAC and makes a determination on what substances to propose for inclusion on the list.
- Statute requires that FDA develop the 503A list by regulation (section 503A(c)).

## Rulemaking Process

- On a rolling basis, FDA will publish for comment proposed rules identifying the substances it believes should be placed on the list and the substances it has evaluated and will not propose for inclusion on the list.
- FDA hopes to publish the first proposed rule addressing the 10 substances that have been presented to PCAC later this year.
- Because of the length of time it takes to complete a rulemaking, multiple rulemakings may be ongoing at the same time.

## Rulemaking Process, cont'd

- After considering public comment on each group of substances, FDA will publish final rules that identify the substances that will be placed on the list and the evaluated substances that will not be placed on the list.
- FDA has not taken action against compounders that compound with bulk drug substances that are not on the list unless the substance raises safety concerns (e.g., domperidone).
- FDA is working on a guidance describing an interim policy regarding compounding with bulk drug substances while FDA is developing the list.

## Removing Substances From the List

- If the USP develops a monograph for a substance on the list, or a drug is approved containing a substance on the list, FDA will remove the substance from the list through one of the ongoing rulemakings because it will no longer need to be on the list and can be used in compounding under section 503A without being on the list.
- Otherwise, FDA will remove substances from the list through rulemaking if it obtains information to suggest that the substances are not appropriate for compounding.

## Reminder of Proposed Criteria:

- The physical and chemical characterization of the substance;
- Any safety issues raised by the use of the substance in compounded drug products;
- Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature; and
- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists.
- No single criterion is dispositive; FDA will consider each criterion in the context of the others and balance them on a substance-by-substance basis.

# Brilliant Blue G

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Wiley A. Chambers, MD, (Clinical Reviewer), Supervisory  
Medical Officer**

**Division of Transplant and Ophthalmology Products**

**Norman Schmuff, PhD, (Chemistry Reviewer), Associate  
Director for Science, Office of Process and Facilities**

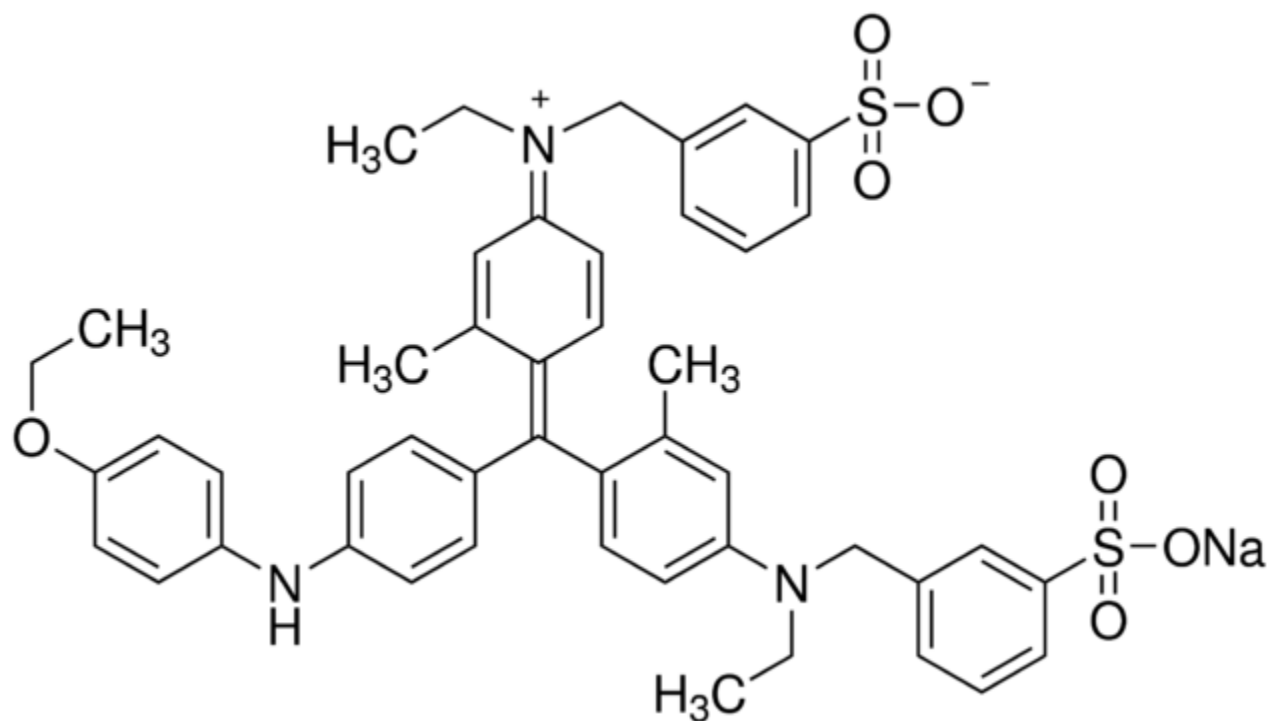
**Aaron Ruhland, PhD, (Pharmacology Reviewer),  
Toxicologist**

**Division of Transplant and Ophthalmology Products**

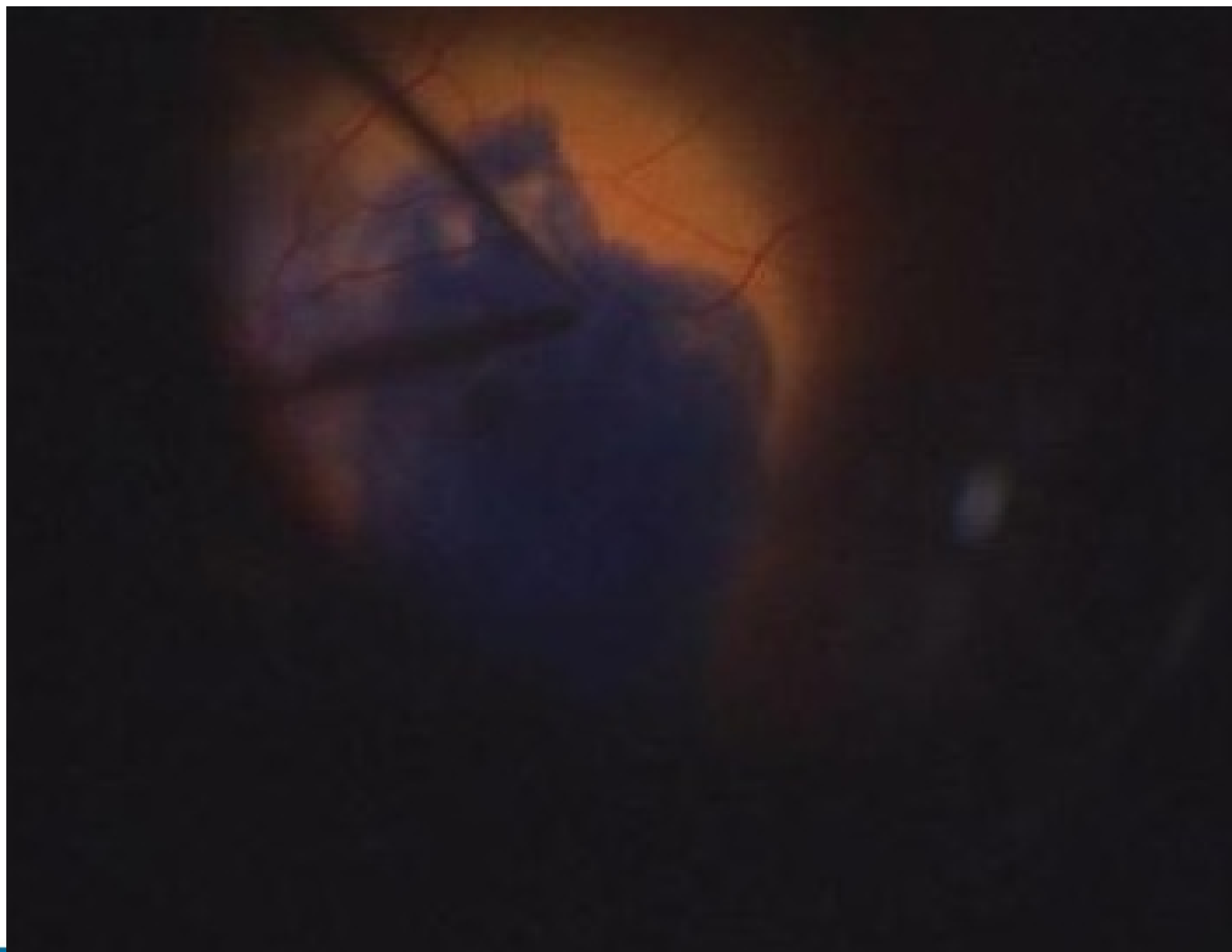
## Brilliant Blue G

Used in staining for visualization during  
ophthalmic procedures

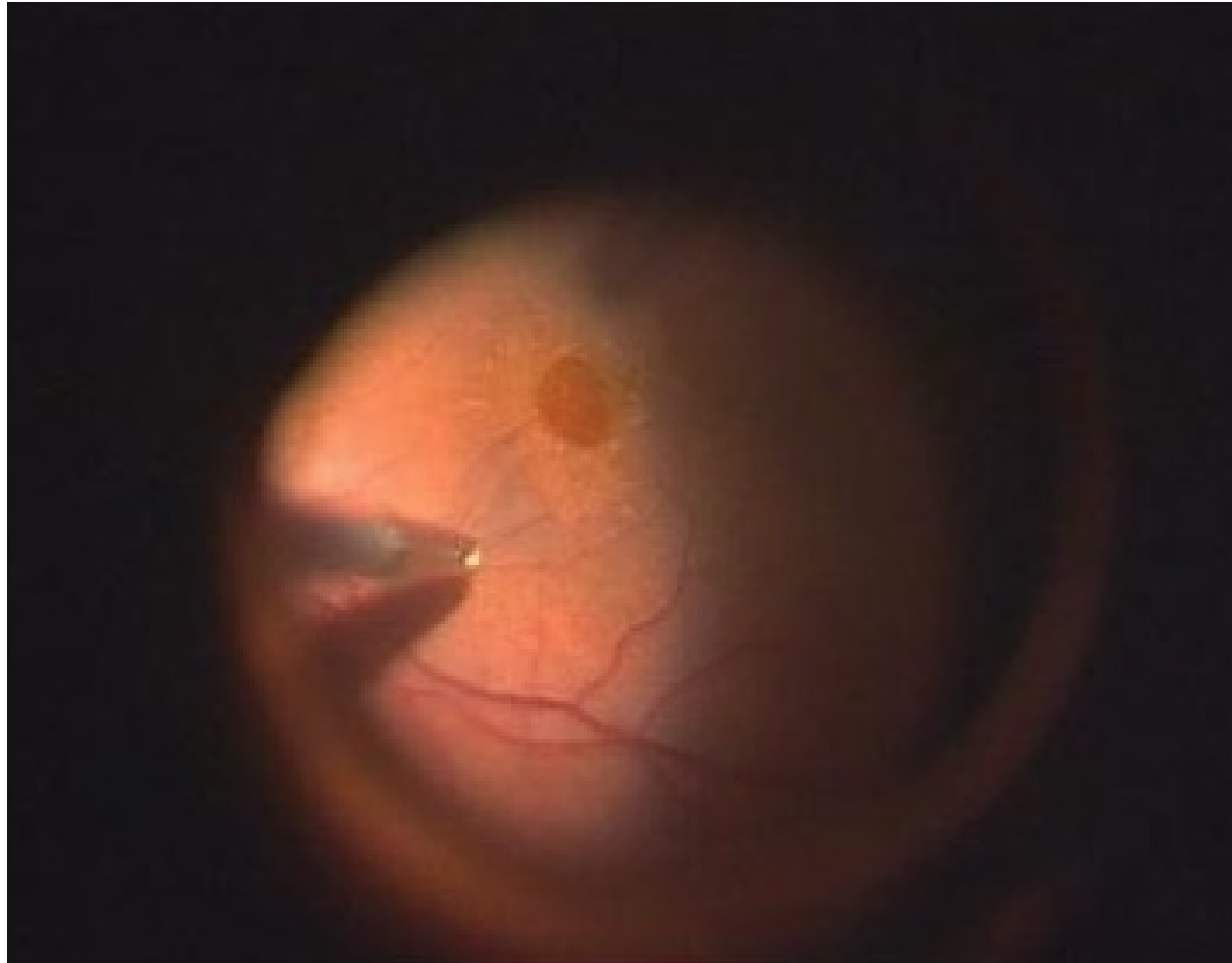
# Brilliant Blue G



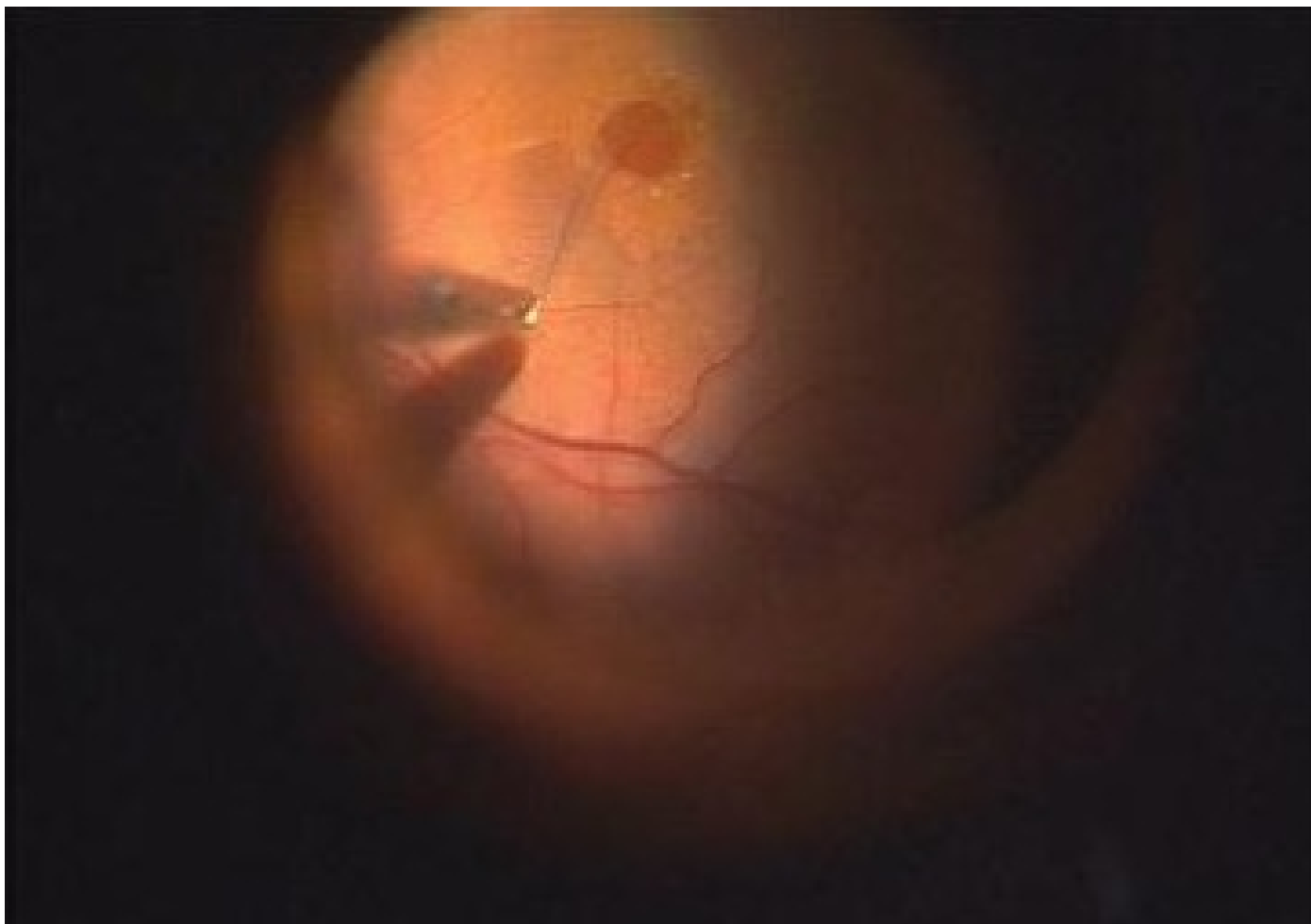
# Brilliant Blue G - Injection



# Brilliant Blue G – Membrane Peeling



# Brilliant Blue G – Membrane Peeling



# Brilliant Blue G

**Stability:** Good

**Probable routes of API synthesis:** Likely route of synthesis from 4-ethoxyaniline and Guinea green 2G

**Physicochemical characteristics pertinent to product performance:** None since the product is a solution

# Brilliant Blue G

**Likely impurities:** The two starting materials may be left as impurities.

**Toxicity of impurities:** A no-observed effect level for 4-ethoxyaniline was reported to be 10 mg/kg/day.

**Conclusion:** Brilliant Blue G is well characterized, chemically and physically.

# Brilliant Blue G

## Nonclinical Assessment - 1

**Pharmacology:** Brilliant Blue G is a common laboratory reagent used for protein visualization.

**Safety Pharmacology:** No information was found related to the standard battery of pharmacology/toxicology safety studies including cardiovascular safety, respiratory safety, or neurobehavioral safety.

### **Acute Toxicity:**

- No studies of acute toxicity due to systemic administration
- In rats, following vitrectomy surgery and intravitreal administration of Brilliant Blue G, no toxic effects observed over a period of 2 months

# Brilliant Blue G

## Nonclinical Assessment - 2

### Carcinogenicity

- Brilliant Blue G at levels greater than or equal to 0.1% has not been identified as a known or anticipated carcinogen, but there are no formal studies. The product is typically used at either 0.025% or 0.05%.

### Mutagenicity

- Brilliant Blue G was found to be mutagenic to the TA98 strain of *Salmonella typhimurium* with and without S9 metabolic activation at a concentration of 0.1%.

# Brilliant Blue G

## Nonclinical Assessment - 3

The potential concern of mutagenicity is mitigated in clinical use because the dye is immediately washed out of the eye after administration, and tissue that is stained with the dye is removed as part of the surgical procedure.

# Brilliant Blue G

## Nonclinical Assessment - Conclusions

Available nonclinical data, although limited, indicate that intravitreal, intracameral or sub-retinal injections of Brilliant Blue G, respectively, did not produce ocular toxicity in rats.

# Brilliant Blue G- Human Safety Data

## Adverse Reactions

- Adverse reactions reported in the literature were more likely to be complications of the surgical procedures for which Brilliant Blue G was used.
- Only exceptions were rare reports of inadvertent staining of other structures
- Single case series of fungal contamination traced to compounding pharmacy
  - We do not have any information on whether Brilliant Blue G is any more or less susceptible to bacterial or fungal contamination than other products used for intravitreal administration.

# Brilliant Blue G: Clinical Trials

Multiple clinical trials have been published supporting the safety and efficacy of Brilliant Blue G when used for ophthalmic visualization, for example:

- Caramoy et al. 2012. Randomized single-center, 2-arm evaluating functional outcomes of macular holes and pucker in 56 patients undergoing internal limiting membrane peeling (Brilliant Blue vs Indocyanine Green)
- Williamson TH and Lee E. 2014. 351 consecutive primary macular hole surgeries, prospectively collected outcomes analyzed in relation to staging and use of Indocyanine Green or Brilliant Blue

## Brilliant Blue G: Clinical Trials (*cont.*)

- Dhananjay et al. 2011. Comparison of Brilliant Blue G, Trypan Blue and Indocyanine Green dyes to assist internal limiting membrane peeling in 50 eyes of 50 patients.
- Baba T et al. 2012. Comparison of Brilliant Blue and Indocyanine Green in 63 eyes of 63 consecutive vitrectomies for macular holes.

## Brilliant Blue G: Clinical Trials *(cont.)*

- Kadonosono K et al. 2013. Evaluation of the difference in color contrast between Indocyanine Green and Brilliant Blue during internal limiting membrane peeling in 40 eyes.
- Totan et al. 2015. Evaluation of the potential safety and efficacy of Brilliant Blue G staining of the internal limiting membrane under air infusion in 63 patients.

## Brilliant Blue G

**Conclusion from the Literature:** Published clinical trials adequately describe the safety and efficacy of Brilliant Blue G in staining for visualization in ophthalmic surgical procedures.

# Brilliant Blue G

## Historical Use in Compounding

Brilliant Blue G has been compounded for ophthalmic use since approximately 2006.

# Alternatives for Staining the Internal Limiting Membrane

- Trypan blue ophthalmic solution, approved for staining the internal limiting membrane
- Indocyanine green, approved for intravenous use, is sometimes used off-label for this indication.

# Alternatives for Staining the Lens Capsule

Trypan blue ophthalmic solution, approved for staining the lens capsule

# Alternatives for Staining

- The absorption spectrum for Brilliant Blue G differs from that of the approved product
  - Different reflected wavelength of light (different shade of blue)
  - Different degree of contrast between the stained tissue and the unstained tissue
  - Depending on the surrounding anatomic structures, wavelength needed to visualize the structure being removed may vary
- To remove the internal limiting membrane, many surgeons prefer Brilliant Blue G

# Brilliant Blue G Conclusions- 1

- Brilliant Blue G is well characterized physically and chemically and can be compounded into a sterile drug dosage form for intravitreal use.
- Brilliant Blue G has been used in staining for visualization during ophthalmic procedures since approximately 2006.
- Clinical trials have shown that, under certain circumstances, it is more effective as a stain for visualization during ophthalmic procedures than the approved alternative.

## Brilliant Blue G Conclusions- 2

The potential mutagenic and carcinogenic risks are mitigated in clinical use because the dye is immediately washed out of the eye after administration, and tissue that is stained with the dye is removed as part of the surgical procedure.

## Recommendation

**We recommend that Brilliant Blue G be placed on the list of bulk substances that may be used for compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.**

# Tranilast

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Kathleen M. Donohue, MD (Clinical Reviewer)**

**Division of Pulmonary, Allergy, and Rheumatology Products**

**Eleni Salicru, PhD (Nonclinical Reviewer)**

**Division of Pulmonary, Allergy, and Rheumatology Products**

**Xinming Liu, Ph.D. (Pharmaceutical Quality Reviewer)**

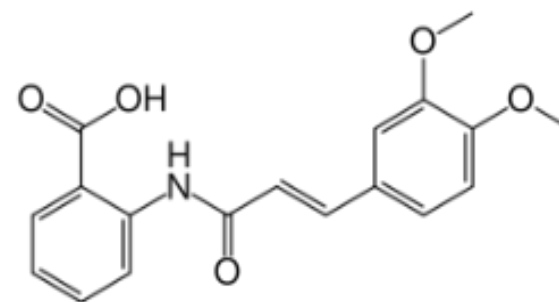
**Office of Pharmaceutical Quality**

# Tranilast: Overview

- Nominated for various uses, including allergic disorders, arthritis, keloids, scarring, and dry eye syndrome
- Evaluation Factors
  - Physical and chemical characterization
  - Nonclinical assessment
  - Human safety data
  - Effectiveness for asthma, allergies, and arthritis
- Keloids, scarring, and ophthalmic uses will be covered separately

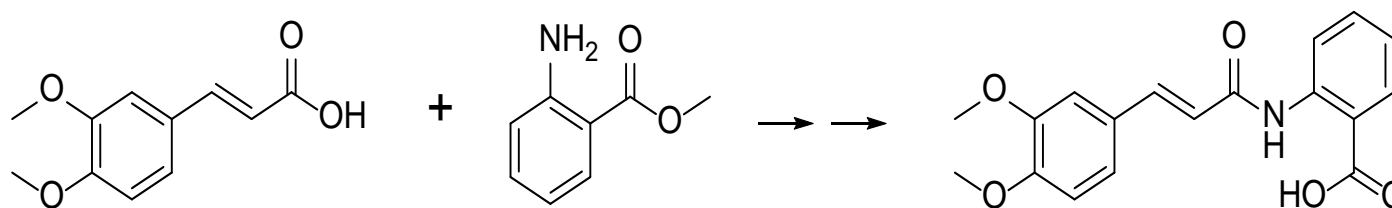
# Physical and Chemical Characterization – 1

- **Formula:**  $C_{18}H_{17}NO_5$
- **Molecular Weight:** 327.33
- **Melting Point:** 166-168 °C
- **Crystal Forms:** Five polymorphic forms
- **Solubility:** Practically insoluble in water
- **Stability:** Stable more than 2 years at -20 °C in crystalline state, unstable in solution under UV and natural sunlight
- **Structure Characterization:** Well characterized



# Physical and Chemical Characterization – 2

- **Probable synthetic route:**



- **Likely impurities:** starting materials, reaction intermediates and the degradation byproducts
- **Conclusion:** The crystal polymorphism of tranilast may impact the performance of formulations

# Nonclinical Assessment - 1

**Pharmacology:** In animal models, tranilast inhibits (1) chemical mediators from mast cells; (2) anaphylaxis; (3) transforming growth factor beta; and (4) accumulation of collagen in granulation tissue

**Safety Pharmacology:** No publicly available data

## **Acute Toxicity:**

- Clinical signs included general depressed activity, respiratory depression, secretion of tears, dermatitis after systemic exposure, and/or eyelid drooping
- Intraperitoneal  $LD_{50} = 395$  mg/kg in rat
- Oral  $LD_{50} = 1100$  mg/kg in rat
- Subcutaneous  $LD_{50} = 2630$  mg/kg in mouse and 3060 mg/kg in rat

# Nonclinical Assessment - 2

## Repeat-Dose Toxicity

- Rats given oral tranilast for 5 weeks at 200, 400, and 800 mg/kg/day
  - 4 deaths in high-dose group with histopathological findings in liver, spleen, kidneys, heart, lungs, and adrenal glands
  - Animals in mid- and high-dose groups (that survived) had statistical differences for several hematology and clinical chemistry parameters (e.g., decreased RBCs, increased ALP)
  - At time of death, organ weight changes were noted for pituitary gland, thymus, lungs, liver, spleens and adrenals; macroscopic or histopathological findings not evident

**Chronic Toxicity, Mutagenicity, Developmental and Reproductive Toxicity, Carcinogenicity, Toxicokinetics:** No publicly available data

## Nonclinical Assessment - 3

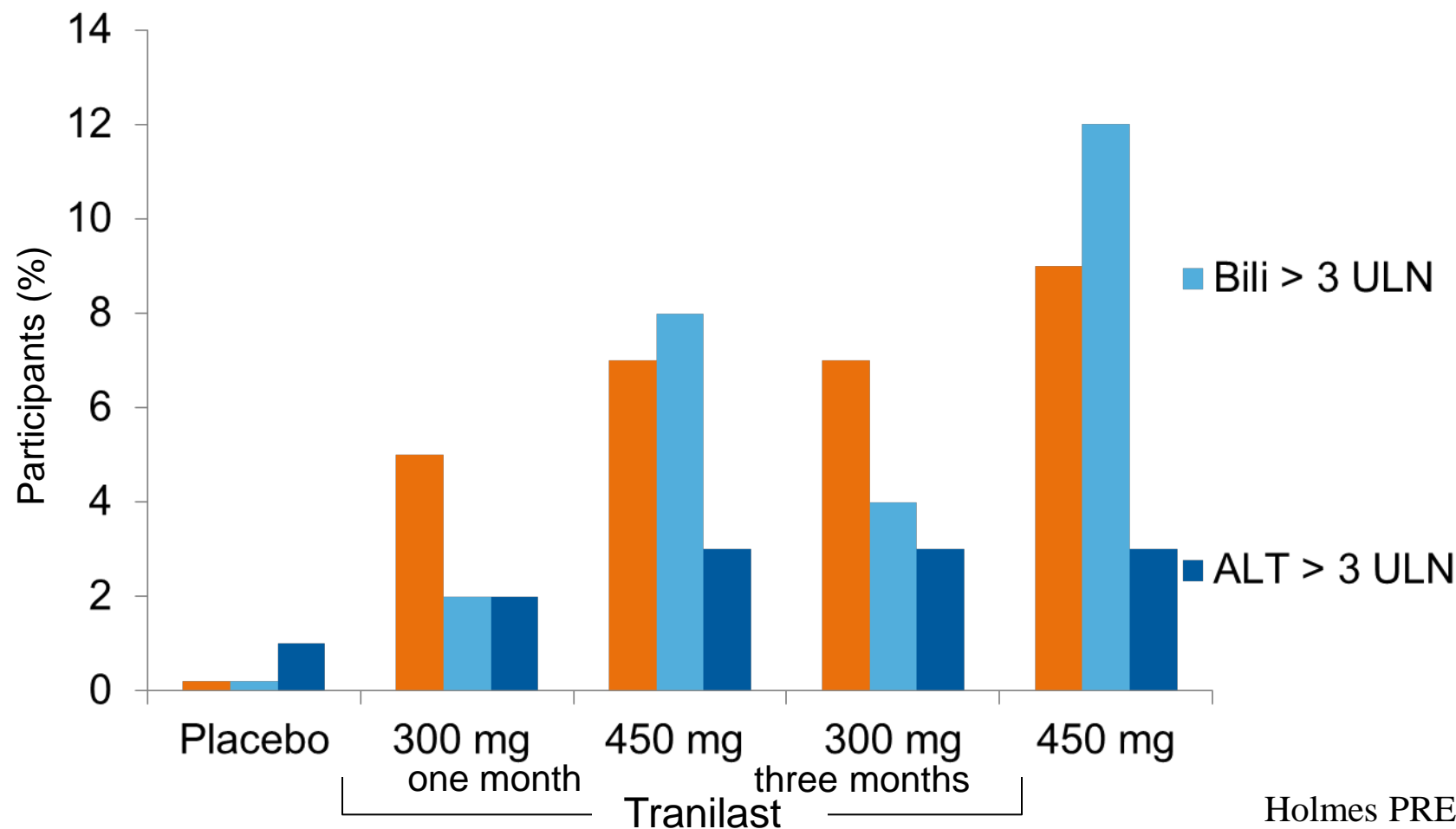
**Conclusions:** Limited, publicly available, nonclinical information for tranilast, thus preventing a comprehensive nonclinical assessment for its use in compounding

# Human Safety Data – 1: PRESTO Trial

<b>Design</b>	R, DB, PC
<b>N</b>	11,484
<b>Endpoint</b>	Coronary restenosis
<b>Dose</b>	300 or 450 mg PO TID
<b>Duration</b>	1 or 3 months
<b>Safety</b>	Liver function tests showed abnormalities in 11% of Tranilast subjects; dose- and duration-related anemia, renal failure, rash, and dysuria

Holmes 2002  
Tamai 1999  
Kosuga 1997

# Human Safety Data – 2: Tranilast Liver Toxicity



Holmes PRESTO 2002

## Human Safety Data – 3: Tranilast Liver Toxicity *(cont.)*

- At least one liver function test result  $> 3$  times the upper limit of normal (ULN)  
and
- Either alkaline phosphatase or bilirubin  $> \text{ULN}$

# Efficacy: Asthma and Allergies

Author	Design	N	Indication	Dose	Route	Duration	Efficacy
Ukai 1993	R	38	allergic rhinitis	300mg/ day	Oral	n/a	sneezing & nasal congestion
Okuda 1984	DB, C	302	allergic rhinitis	n/a	n/a	n/a	symptoms
Suzuki 1989	n/a	18	asthma	100mg/ day	Oral	± 3 months	bronchial hyper reactivity
Shioda 1979	R, DB, PC	277	pediatric asthma	5- 10mg/ kg/day	Oral	1.5 months	asthma symptoms

# Efficacy: Arthritis

No human data

# FDA Approved Alternatives

## Asthma and Allergies

- Ocular, nasal, oral antihistamines
- Ocular, nasal, inhalational corticosteroids
- Biologic
- Mast cell stabilizers
- Leukotriene modifiers

## Arthritis

- TNF inhibitors
- Anti-cytokine therapies
- Rituximab
- Methotrexate, sulfasalazine, hydroxychloroquine

Wheatley 2015  
Singh 2012

# Historical Use of Tranilast in Compounding – 1



- Length of time of use in U.S. is unknown
- Currently available from compounders:
  - Oral, intranasal, topical creams, dental rinse
  - Scars, eczema, psoriasis, allergies, “fly safe”

# Historical Use of Tranilast in Compounding – 2

- Product developed by Kissei Pharmaceuticals in 1982 in South Korea and Japan
- Approved in South Korea and Japan for asthma, keloids



## Recommendation

**We do *not* recommend that Tranilast be placed on the list of bulk drug substances that may be used for compounding under section 503A of the Federal Food, Drug, and Cosmetic Act for any allergy or rheumatology indication.**



# Tranilast

**Pharmacy Compounding Advisory Committee Meeting  
June 17, 2015**

**Snezana Trajkovic, MD  
(Clinical Reviewer), Medical Officer,  
Division of Dermatology and Dental Products**

## Tranilast Uses

Marketed in Japan since 1993 for the treatment of:

- Keloids
- Hypertrophic scars

# Keloids



A  
Sachiko Koike et al. Nd:YAG Laser Treatment for keloids and Hypertrophic scars: An Analysis of 102 Cases. *Plast Reconstr Surg Glob Open*. 2014 Dec; 2(12):e272.

- Bosselated tumors that project above the level of the surrounding skin
- Characterized by excessive accumulation of extracellular matrix, mostly type I and III collagen
- Grow continuously and beyond the borders of the original wound, and do not regress with time

# Hypertrophic Scars



- Elevated scars that do not spread into surrounding tissues
- Characterized by excessive deposition of extracellular matrix and by persistent inflammation and fibrosis
- Often regress spontaneously

Rabello et al. Update on hypertrophic scar treatment.  
Clinics 2014; 69 (8): 565-573

# Available Treatments

## Keloids and Hypertrophic Scars

- No FDA approved drugs or biologics for the treatment of keloids and hypertrophic scars
- [ClinicalTrials.gov](http://ClinicalTrials.gov) lists 9 ongoing clinical trials using other drugs for the treatment of keloids and hypertrophic scars

# Available Treatments

## Keloids and Hypertrophic Scars (*cont.*)

- Treatment modalities used in clinical practice:
  - Silicone gel sheeting, silicone gels
  - Pressure garments
  - Intralesional injections with corticosteroids, bleomycin, 5-fluoruracil
  - Surgery
  - Radiotherapy
  - Laser

# Tranilast - Human Safety

## Keloids and Hypertrophic Scars

### Topical administration

Shigeki et al. (1997): Open-label study of treatment of keloids and hypertrophic scars using iontophoresis in 4 subjects. No adverse reactions were reported.

# Tranilast- Human Safety

## Keloids and Hypertrophic Scars (*cont.*)

### Oral administration

Nanba et al. (1992): multi-center, blinded to dose study in 263 subjects with keloids and hypertrophic scars. Subjects were treated with 3 doses of oral tranilast: 2.5mg/kg/day; 5mg/kg/day; and 7.5mg/kg/day. Adverse reaction rates reported: 8.3%; 7.5% and 11.0%, respectively. Adverse reactions not specified.

# Tranilast - Human Safety

## Other Indications

- Holms et al. (2002), PRESTO trial:
  - LFT elevation
  - Increased creatinine
  - Anemia
- Adverse reactions from case reports on systemic use:
  - Immune thrombocytopenia
  - Eosinophilic polymyositis
  - Eosinophilic cystitis.

# Tranilast - Efficacy

## Keloids and Hypertrophic Scars

### Literature Reports

Author	Design	N	Route	Duration
Nanba 1992	Open label; blinded to dose	263	Oral	12 weeks
Shigeki 1997	Open label	4	Topical	7-12 treatments
Muraoka 2002	Case series	2	Oral	4 months
Banov 2014	Case series	1	Topical	3 weeks

# Conclusion - Tranilast Safety Treatment of Keloids and Hypertrophic Scars

- Available safety information on use of oral or topical tranilast in the treatment of keloids and hypertrophic scars is based on uncontrolled clinical studies in small number of patients, case series, and case reports.
- Available safety information from well-controlled clinical trials using oral tranilast in other indications suggests potential for liver injury.

# Conclusion - Tranilast Efficacy Treatment of Keloids and Hypertrophic Scars

- There are no reports of well-controlled clinical trials in the treatment of keloids and hypertrophic scars.
- Efficacy information is based on reports from a dose-blind uncontrolled clinical study, a small open-label study, and two small case series.

# Recommendation - Tranilast Treatment of Keloids and Hypertrophic Scars

We recommend that tranilast ***not*** be placed on the list of bulk substances that may be used for compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.

# Tranilast Ophthalmic Solution

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Wiley A. Chambers, MD, (Clinical Reviewer)  
Supervisory Medical Officer  
Division of Transplant and Ophthalmology Products**

# Tranilast Ophthalmic Solution

- Nominated for use in the treatment of dry eyes
- Approved for use in Japan for the treatment of allergic conjunctivitis
- No published studies found involving compounding of tranilast into an ophthalmic solution

## Tranilast Ophthalmic Solution

- Three exploratory studies, one in each of three different indications, have been published using the Japanese approved product
  - Ocular graft versus host disease
  - Postoperative trabeculectomy surgery
  - Postoperative cataract surgery

## Tranilast Ophthalmic Solution

**Ogawa Y et al, 2010:** 18 patient, uncontrolled, case series, involving treatment of chronic graft versus host ocular disease

- No serious adverse events
- Decrease noted in rose bengal staining, but not in fluorescein staining. This is a similar effect to that seen by water alone.

## Tranilast Ophthalmic Solution

**Tobari et al, 1999:** 35 patient, randomized, vehicle controlled study in postoperative cataract patients to prevent posterior capsular opacification

- No serious adverse events
- Decrease in posterior capsular opacification, but no difference in visual acuity between groups.

## Tranilast Ophthalmic Solution

**Chibara et al, 2002:** 52 patient, randomized, vehicle controlled study in postoperative trabeculectomy patients to prevent scarring of the trabeculectomy

- No serious adverse events
- Small decrease in intraocular pressure

## Tranilast Ophthalmic Solution

One study has been published using a Brazilian manufactured ophthalmic product

- Postoperative pterygium surgery

## Tranilast Ophthalmic Solution

**Almeida et al, 2015:** 50 patient, randomized, vehicle controlled study in postoperative pterygium surgery to prevent recurrence of pterygium

- No serious adverse events
- No difference between groups

# Tranilast Ophthalmic Solution

No published studies found to support the Japanese approved indication for allergic conjunctivitis

# Products approved for use in allergic conjunctivitis in the United States

<b>Lastacraft</b>	<b>Alcaftadine ophthalmic solution</b>	<b>Ocular itching in patients with allergic conjunctivitis</b>
<b>Optivar</b>	<b>Azelastine Hydrochloride ophthalmic solution</b>	<b>Ocular itching in patients with allergic conjunctivitis</b>
<b>Bepreve</b>	<b>Bepotastine ophthalmic solution</b>	<b>Ocular itching in patients with allergic conjunctivitis</b>
<b>Elestat</b>	<b>Epinastine Hydrochloride ophthalmic solution</b>	<b>Ocular itching in patients with allergic conjunctivitis</b>
<b>Alocril</b>	<b>Nedocromil sodium ophthalmic solution</b>	<b>Ocular itching in patients with allergic conjunctivitis</b>
<b>Pataday</b>	<b>Olopatadine hydrochloride ophthalmic solution</b>	<b>Ocular itching in patients with allergic conjunctivitis</b>
<b>Alamast</b>	<b>Pemirolast potassium ophthalmic solution</b>	<b>Ocular itching in patients with allergic conjunctivitis</b>
<b>Acular</b>	<b>Ketorolac tromethamine ophthalmic solution</b>	<b>Ocular itching in patients with allergic conjunctivitis</b>
<b>Emadine</b>	<b>Emedastine difumarate ophthalmic solution</b>	<b>Allergic conjunctivitis</b>
<b>Alrex</b>	<b>Loteprednol etabonate ophthalmic suspension</b>	<b>Allergic conjunctivitis</b>
<b>Patanol</b>	<b>Olopatadine hydrochloride ophthalmic solution</b>	<b>Allergic conjunctivitis</b>

## Tranilast Ophthalmic Solution Conclusions

- Tranilast is well characterized physically and chemically and marketed in Japan and other countries for allergic conjunctivitis. In the US, alternative products are available for allergic conjunctivitis.
- Exploratory studies with commercially available Tranilast ophthalmic solutions have been conducted outside the US.
- No published studies were found using a compounded formulation of Tranilast ophthalmic solution.

## Recommendation

We do not recommend that Tranilast be placed on the list of bulk substances that may be used for compounding under section 503A of the Federal Food, Drug, and Cosmetic Act for any ophthalmic indication.

# N-Acetyl-D-Glucosamine

**Pharmacy Compounding Advisory Committee Meeting  
June 17, 2015**

**Patricia Brown, MD, FAAD (Clinical Reviewer), Medical Officer  
Division of Dermatology and Dental Products**

**Hamid Shafei, PhD, (Chemistry Reviewer), Product Quality  
Reviewer, Office of New Drug Products, Division II, Branch V**

**Doanh Tran, PhD, (Clinical Pharmacology Team Leader)  
Pharmacologist, Division of Clinical Pharmacology, III**

**Jiaqin Yao, PhD (Pharmacology Reviewer), Pharmacologist  
Division of Dermatology and Dental Products**

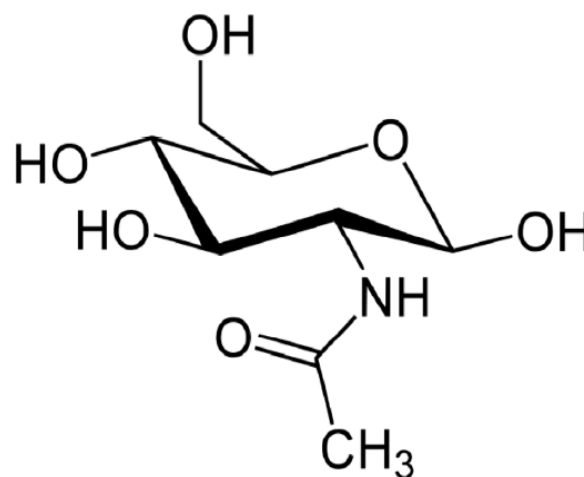
# N-Acetyl-D-Glucosamine: Uses

Used to treat hyperpigmentation of the skin

- Hyperpigmentation
  - Increase in melanin production
  - Change in density of activated melanocytes
  - Deposition of substances in dermis

# N-Acetyl-D-Glucosamine

- $C_8H_{15}NO_6$
- 221.21 g/mol
- Melting point: 221°C



# N-Acetyl-D-Glucosamine

**Stability:** Stable in the solid state under ambient conditions and in solution at neutral pH

**Probable routes of API synthesis:** Acid hydrolysis and/or enzymatic hydrolysis of chitin (a carbohydrate)

**Physicochemical characteristics pertinent to product performance:** Currently insufficient information about impact of API's particle size and polymorphism on bioavailability

# N-Acetyl-D-Glucosamine

## **Likely impurities:**

- Residual carbohydrates
- Residual solvents
- Heavy metals
- Microbial content, yeast or mold

**Toxicity of impurities:** Residual carbohydrates not generally considered toxic. Testing for other potential impurities performed by manufacturers

**Conclusion:** Well-established chemical entity, marketed in a solid dosage form as a dietary supplement. Likely to be available with a reasonable purity

# N-Acetyl-D-Glucosamine

## Nonclinical Assessment - 1

**Pharmacology:** Inhibits the conversion of prototyrosinase to tyrosinase to reduce hyperpigmentation

**Safety Pharmacology:** Endogenous compound. No safety pharmacology study has been found.

**General Toxicology:** The no observed adverse effect level (NOAEL) was 5% in the diet of rats treated for up to 52 weeks.

# N-Acetyl-D-Glucosamine

## Nonclinical Assessment - 2

**Mutagenicity:** Negative in the Ames test and Comet assay.

**Developmental and Reproductive Toxicity:** No developmental and reproductive toxicology study has been found.

**Carcinogenicity:** Oral treatment did not cause any carcinogenic effects in rats.

# N-Acetyl-D-Glucosamine

## Human Safety Data - 1

### Adverse Events (AEs)

## Clinical Trials

### Systemic Administration

- Anderson et al. (2005): Glucosamine - 9.7 g IV over 6 hours in 10 healthy volunteers; no reported side effects

### Osteoarthritis

- Towheed and Anastassiades (1999): Glucosamine sulfate - 1208 subjects with osteoarthritis, 500 mg orally 3x daily, mean period 50 days; 88% of subjects - no side effects; 12% mild side effects, primarily GI

# N-Acetyl-D-Glucosamine

## Human Safety Data – 2

### Osteoarthritis (*cont.*)

- Reginster et al. (2001): 3 year, randomized, double-blind, placebo-controlled trial – 212 subjects w/ knee osteoarthritis (age 51 and older); 1500 mg glucosamine sulfate daily or placebo – no substantial differences between groups in AEs
- Anderson et al. (2005): review of multiple trials, oral glucosamine (1500 mg/day); no adverse effects on blood chemistry, hematology, U/A, occult blood, or CV parameters
- Towheed et al. (2005): Cochrane review of 25 RCT, glucosamine as safe as placebo

# N-Acetyl-D-Glucosamine

## Human Safety Data - 3

### Hyperpigmentation

- Bissett et al. (2007): 8 week, double-blinded, vehicle controlled, left-right, randomized, split-face trial – 50 subjects (ages 25-55); specific adverse events not listed
- Kimball et al. (2010): 10 week, double-blind, vehicle controlled, parallel group trial prospective, 202 subjects (women ages 40-60); 4 subjects in 2% NAG + 4% niacinamide group experienced skin irritation; 3 subjects in vehicle group experienced skin irritation

# N-Acetyl-D-Glucosamine: Efficacy - 1

- Hyperpigmentation

- Bissett et al. (2007): double-blinded, placebo controlled, split face trial 50 Japanese women (ages 25-55). Inclusion: solar lentigo, melasma, freckles both sides of face. 2% NAG improved facial hyperpigmentation, computer image analysis ( $p = 0.089$ )
- Bissett et al. (2007); double-blinded, placebo controlled, split face trial 35 Caucasian women (ages 35-65). Inclusion: solar lentigo both sides of face. Hyperpigmentation measured by computer image analysis and assessment of digital images. Efficacy: 2% NAG + 4% niacinamide > 4% niacinamide > vehicle control, statistically significant for combo vs vehicle control

## N-Acetyl-D-Glucosamine: Efficacy - 2

- Hyperpigmentation (*cont.*)
  - Kimball et al. (2010): double-blinded, vehicle controlled, parallel group, 202 subjects (women ages 40-60), irregular hyperpigmentation due to solar lentigines, 2% NAG + 4% niacinamide vs vehicle; computer image analysis, visual grading, and melanin-specific image analysis for melanin spot fraction and melanin chromophore evenness. Authors found 2% NAG + 4% niacinamide significantly more effective than vehicle control.

# N-Acetyl-D-Glucosamine

## Historical Use in Compounding

- Used topically for hyperpigmentation since mid 2000s
- Use for treatment of hyperpigmentation appears generally accepted by dermatology community
- We have not found evidence that topical NAG is marketed in foreign countries; however, oral glucosamine is marketed in numerous foreign countries

# Hyperpigmentation

## Alternative approved therapies

- **Combination product:** Hydroquinone 4% (with 0.01% fluocinolone & .05% tretinoin) approved for treatment of melasma in adults. AEs: exogenous ochronosis, endocrine effects from topical steroid, irritation, hypersensitivity
- **Combination product:** Mequinol 2% (with 0.01% tretinoin) approved for treatment of solar lentigines in adults. AEs: erythema, irritation, augmented photosensitivity; (product discontinued, but NDA still in effect)
- **Tretinoin** cream, gel, solution, multiple strengths approved as adjunctive agent in mitigation of fine wrinkles, mottled hyperpigmentation, tactile roughness in adults. AEs: irritation, increased sun sensitivity, known teratogen

# N-Acetyl-D-Glucosamine

## Conclusion

- Well-established chemical entity
- Endogenous compound; topical use associated with minor and infrequent side effects
- Controlled clinical trials suggest positive treatment effect
- May be useful alternative to therapies containing hydroquinone and tretinoin

## Recommendation

**We recommend that N-Acetyl-D-Glucosamine for topical use be placed on the list of bulk substances that may be used for compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.**

# Oxitriptan (5-Hydroxytryptophan (5-HTP))

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Glenn Mannheim, MD, (Clinical Reviewer)**

**Division of Psychiatry Products**

**David Claffey, PhD (Chemistry Reviewer)**

**Office of Pharmaceutical Quality**

**Praveen Balimane, PhD, (Clinical Pharmacology Reviewer)**

**Division of Clinical Pharmacology I**

**Jerry M. Cott, PhD (Pharmacology/Toxicology Reviewer)**

**Division of Psychiatry Products**

**Courtney Suggs, PharmD, MPH (Pharmacovigilance Reviewer)**

**Division of Pharmacovigilance I**

# Indications for Compounding

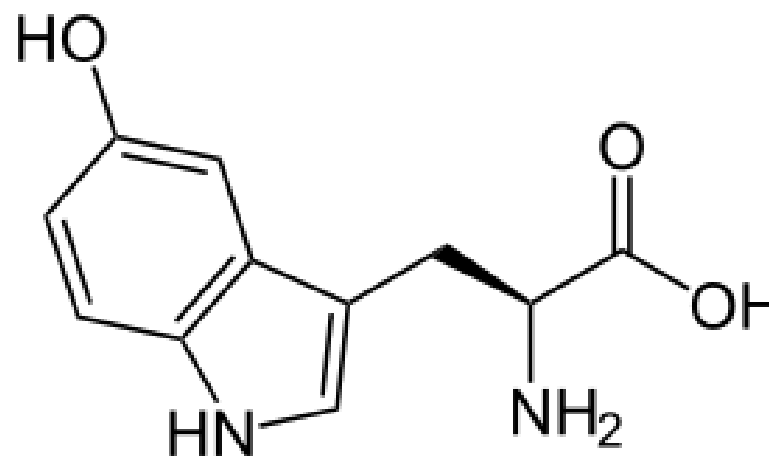
- Depression
- Sleep disorders

# Oxitriptan

- Hydroxylated form of a naturally occurring amino acid, tryptophan
- A chemical precursor in the biosynthesis of serotonin and melatonin from tryptophan

# Oxitriptan

- 5-Hydroxytryptophan
- $C_{11}H_{12}N_2O_3$
- 220.2 g/mol
- Melting point: 298° C
- Crystalline



# Oxitriptan

**Stability:** No literature reports of stability issues when stored under typical room temperature conditions

**Probable routes of API synthesis:** Extracted from *Griffonia simplicifolia* seeds. A literature search did not reveal any public information on the extraction procedures.

# Oxitriptan Impurities

**Likely impurities:** Possible impurities from seed extraction

**Toxicity of impurities:** Unknown as the exact impurities are not known

**Conclusion:** No indications of chemical instability or that impurities present significant toxicity

# Clinical Pharmacokinetics

- 5-HTP is well absorbed after oral dosing with an absolute bioavailability of 70%.
- It is absorbed rapidly with a  $T_{\max}$  of 2-3 hrs.
- It has a biological  $T_{1/2}$  of around 6 hrs and, thus, is unlikely to accumulate on repeat dosing when given once-daily or twice daily.
- It demonstrates linear pharmacokinetics in the dose-range of 50 mg to 200 mg.

# Nonclinical Assessment

## Pharmacology

- 5-HTP is a chemical precursor in the biosynthesis of the neurotransmitters serotonin and melatonin from tryptophan.
- 5-HTP crosses the blood–brain barrier and is decarboxylated to serotonin.
- There were no concerns from the minimal available data on safety pharmacology.

# Nonclinical Assessment *(cont.)*

## Toxicology

- There are no data on repeat dose toxicity, carcinogenicity, embryo-fetal, or post-natal reproduction.
- There were no concerns from the minimal available data on acute toxicity, mutagenicity, or teratogenicity.

# Clinical Assessment: Efficacy

## Clinical Trials for Depression

Shaw KA et al. (Cochrane Rev; 2002):

- 2 out of 108 depression trials with 5-HTP are randomized, double-blind, placebo controlled trials with some depression measures.
- Only 64 subjects in these two trials exposed to oxitriptan or tryptophan for up to 10 weeks.
- The studies showed some efficacy for oxitriptan in depression.
- Limitations: small sample size of placebo controlled trials

# Clinical Assessment: Efficacy *(cont.)*

## Clinical Trials for Depression *(cont.)*

Jangid P et al. (2013):

- A 8-week trial of L-5-HTP vs. fluoxetine using Hamilton Depression Scale and a Clinical Global Improvement Scale in 60 subjects with mild, depression showed significant reduction in HAM-D scores in both groups.
- Limitation: no placebo control group.

**No long-term efficacy and safety trials were identified.**

# Clinical Assessment: Efficacy *(cont.)*

## Clinical Trials for Insomnia:

- Bruni O et al. (2004): Open label study suggesting benefit in pediatric sleep terrors
- Shell W et al. (2010): Double-blind study comparing gamma-aminobutyric acid (GABA) and oxitriptan combination to placebo in 18 subjects with insomnia (9 per group), showed significant decreased time to sleep onset and increased sleep duration compared to placebo. Not useful for efficacy given small sample and combination product.
- Limitations: few studies, open-label, and small sample size

# Clinical Assessment: Safety

## Common adverse reactions

- Nausea, diarrhea, vomiting, epigastric pain, anorexia, headache, dizziness

## Potential risk

- Serotonin syndrome: may occur when combined with certain antidepressant drugs (selective serotonin reuptake inhibitors or monoamine oxidase inhibitors) based on the mechanism of action.

# Clinical Assessment: Safety *(cont.)*

## Other Potential Safety Issues

- 1989-1990: L-tryptophan was associated with eosinophilia–myalgia syndrome (EMS) in over 1500 people leading to over 30 deaths probably related to contamination by ethylidene-bis-tryptophan and methyltetrahydro-beta-carboline-carboxylic acid from a single manufacturer.
- The risk of EMS seems remote for oxitriptan because of the differences in production methods today and the lack of subsequent reports of EMS connected with oxitriptan.

# FDA Adverse Event Reporting System (FAERS) Search - Oxitriptan

- Search yielded 15 cases
- One of the 15 cases reported the use in a compounded product
- Reported reasons for use: depression, insomnia, epilepsy, convulsions, 6-pyruvoyl tetrahydropterin deficiency (PTPS – 3 cases)
- Reported adverse events: diarrhea, nausea, vomiting, abdominal pain, serotonin syndrome, somnolence
- Many cases reported multiple concomitant medications and medical conditions

# Limitations of FAERS Data

- Passive surveillance - underreporting
- Quality of reports is variable (i.e., missing information)
- FDA does not receive all adverse events that may occur with a product
- Reports on quality issues on bulk ingredients are not usually reported to FAERS. These issues are usually submitted to the Office of Compliance, Office of Unapproved Drugs and Labeling Compliance (OUDLC).

# Historical Use in Compounding

- Approximately 40 years (length uncertain)
- Dietary supplements: 623 products contain 5-HTP (Natural Medicines Comprehensive Database)
- Used in other countries
- Reported uses include: mood disorders; sleep disorders; headaches; fibromyalgia; premenstrual syndrome

# Not Recommended for Depression

- Failure to treat MDD, a serious mental illness, may lead to serious consequences including death.
- The efficacy of oxitriptan in the treatment of depression has not been established by adequately designed clinical trials.
- Multiple effective treatment alternatives (e.g., antidepressants, psychotherapy) are available.

# Not Recommended for Depression *(cont.)*

- Potential risk of serotonin syndrome, a serious, life-threatening drug interaction.
- Medications used to treat depression have been linked to suicidality in young people. No data available to suggest that 5-HTP would be free of similar risks
- **Without proper labeling, neither the prescriber nor the user can be adequately warned of these risks.**

# Not Recommended for Sleep Disorders

- The efficacy of 5-HTP in the treatment of sleep disorders has not been adequately established.
- Multiple alternative FDA-approved therapies are available.
- Sleep disorders are usually not life-threatening conditions.

## Final Recommendation

We recommend that oxitriptan not be placed on the list of bulk substances that may be used for compounding under section 503A of the FD&C Act.

# **Introduction to Conditions Related to Drugs That Are Difficult to Compound**

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Jane A. Axelrad  
Associate Director for Policy, CDER  
And Agency Lead on Compounding**

## Both 503A and 503B Contain Conditions on Difficult to Compound Drugs

### Section 503A:

- To qualify for the exemptions under section 503A, the compounded drug product may not be a “drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product” (section 503A(b)(3)(A) of the FD&C Act).
- Before issuing regulations on demonstrably difficult to compound drugs, FDA must consult the PCAC “unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health” (section 503A(c)(1) of the FD&C Act).

## Both 503A and 503B Contain Conditions on Difficult To Compound Drugs

### Section 503B:

- To qualify for the exemptions under section 503B, an outsourcing facility may not compound a drug identified “on a list published by the Secretary ... of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients, or ... [the drug] is compounded in accordance with all applicable conditions... that are necessary to prevent the drug or category of drugs from presenting the demonstrable difficulties [identified]” (section 503B(a)(6) of the FD&C Act).
- Section 503B has a similar requirement to consult the PCAC before issuing regulations on demonstrably difficult to compound drugs

## 503A Difficult to Compound List History

- At a meeting on July 13 and 14, 2000, the PCAC discussed and provided FDA with advice about the Agency's efforts to develop a list of drugs that present demonstrable difficulties for compounding.
- At the meeting, FDA described its proposed criteria and the categories of drugs that it was considering for the list. A concept paper was published in the docket before the meeting and discussed at the meeting:

<http://www.fda.gov/ohrms/dockets/dockets/00n1357/00n1357.htm>

- Comments were submitted to the docket, but FDA suspended efforts to develop the list after the Supreme Court decision held certain provisions of section 503A unconstitutional in 2002.
- FDA is now beginning again to identify drugs that are difficult to compound under either section 503A or 503B, and revisiting the criteria it will use to develop the list.

# **Demonstrably Difficult to Compound Drug Products**

**Pharmacy Compounding Advisory Committee Meeting  
June 17-18, 2015**

**Cyrus Agarabi, Pharm.D., R.Ph., M.B.A., Ph.D.**

**LCDR., U.S. Public Health Service**

**Division of Biotechnology Review and Research II**

**Office of Pharmaceutical Quality**

**Center for Drug Evaluation and Research**

# Identifying Difficult to Compound Drugs

- To begin the process of identifying which products or categories of drug products are demonstrably difficult to compound, FDA convened an internal Agency work group.
- We identified six criteria to use to evaluate whether a drug product or category of drug products is demonstrably difficult to compound under sections 503A and 503B.

# Proposed Evaluation Criteria

1. Complex Formulation
2. Complex Drug Delivery Mechanism
3. Complex Dosage Form
4. Bioavailability
5. Compounding Process Complexity
6. Physicochemical or Analytical Testing Complexity

## Proposed Evaluation Criteria *(cont.)*

To identify these criteria, we considered attributes related to the difficulty of compounding that could affect a product's safety and efficacy.

# 1. Complex Formulation

- Formulation in which the ingredients are required to have certain unique characteristics or properties that are necessary to achieve and maintain the proper performance of the drug product.
- Examples may include:
  - Crystalline (including polymorphs) or amorphous forms
  - Chirality
  - Particle size

## 2. Complex Drug Delivery Mechanism

- The way in which the drug product is targeted for delivery and/or released from the dosage form in the body to achieve the desired therapeutic effect.
- Examples may include:
  - Coated beads
  - Polymeric matrices
  - Liposomes

### 3. Complex Dosage Form

- Physical dosage units with characteristics that are difficult to consistently achieve and maintain.
- Examples may include:
  - Propellant based aerosolized products
  - Dry powder inhalers

## 4. Bioavailability

- The rate and extent to which the active ingredient, or its active moiety, is absorbed into the body and becomes available at the site of action.
- Examples may include:
  - Characteristics of the API or compounded drug product resulting in inconsistent bioavailability

## 5. Compounding Process Complexity

- Compounding the drug product requires multiple, complicated, or interrelated steps and/or specialized facilities and/or equipment to achieve the appropriate drug product.
- Examples may include:
  - Creating multi-particulate dosage forms of solid oral beads (requires wet granulation, extrusion, spheronization, fluid bed drying, coating or curing before they are processed into the final dosage form)

## 6. Physicochemical or Analytical Testing Complexity

- The challenges presented with confirming the end-product testing for batch-to-batch uniformity, potency, purity, and quality of a drug product.
- Examples may include:
  - Specialized analytical instruments and/or training for identifying constituents of complex mixtures by nuclear magnetic resonance, mass spectrometry, and/or X-ray powder diffraction
  - Cell-based assays for performance characterization

## Application of the Criteria

1. The criteria are not mutually exclusive; a drug product, or category of drug products, may meet one or more of these criteria.
2. These criteria will be considered individually and collectively when evaluating whether a drug product or category of drug products is demonstrably difficult to compound.
3. No single criterion will be considered dispositive.

# Application of Criteria - Example

Example	(1) Complex formulation	(2) Complex drug delivery system	(3) Complex Dosage Form	(4) Bioavailability	(5) Compounding Process Complexity	(6) Testing Complexity
1					Yes	
2	Yes			Yes	Yes	Yes
3	Yes			Yes		

# Approach for Identifying Difficult to Compound Drug Products or Categories of Products

- FDA received 71 nominations for difficult to compound drug products and categories of drug products, and FDA has identified some potential categories separately
- Focus will be on products that are known to be difficult to manufacture with:
  - Evidence in the literature,
  - FDA experience reviewing new and abbreviated new drug applications,
  - Potential to affect the public health.

## Next Steps

- FDA will begin an evaluation of the nominated products and others in the coming months using the criteria discussed today.